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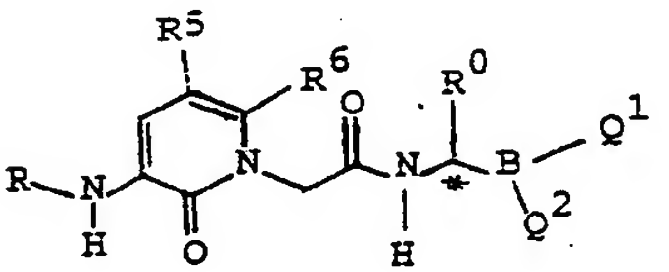

(I)

(57) Abstract

The present invention relates to certain novel heterocyclic derivatives which are 1-pyridylacetamide derivatives of formula (I), set out herein, which are inhibitors of human leukocyte elastase (HLE), also known as human neutrophil elastase (HNE), making them useful whenever such inhibition is desired, such as for research tools in pharmacological, diagnostic and related studies and in the treatment of diseases on mammals in which (HLE) is implicated. The invention also includes intermediates useful in the synthesis of these heterocyclic derivatives, processes for preparing the heterocyclic derivatives, pharmaceutical compositions containing such heterocyclic derivatives and methods for their use.

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ALPHA-AMINOBORONIC ACID PEPTIDES AND THEIR USE AS ELASTASE INHIBITORS

The present invention relates to certain heterocyclic derivatives, in particular, certain 1-pyridylacetamide compounds, which are inhibitors of human leukocyte elastase (HLE), also known as human neutrophil elastase (HNE), making them useful whenever such inhibition is desired, such as for research tools in pharmacological, diagnostic and related studies and in the treatment of diseases in mammals in which HLE is implicated. For example, HLE has been implicated in the pathogenesis of acute respiratory distress syndrome (ARDS), rheumatoid arthritis, atherosclerosis, pulmonary emphysema, and other inflammatory disorders, including airway inflammatory diseases characterized by increased and abnormal airway secretion such as chronic bronchitis and cystic fibrosis. Also, HLE has been implicated in certain vascular diseases and related conditions (and their therapy) in which neutrophil participation is involved or implicated, for example, in hemorrhage associated with acute non-lymphocytic leukemia, as well as in reperfusion injury associated with, for example, myocardial ischaemia and related conditions associated with coronary artery disease such as angina and infarction, cerebrovascular ischaemia such as transient ischaemic attack and stroke, peripheral occlusive vascular disease such as intermittent claudication and critical limb ischaemia, venous insufficiency such as venous hypertension, varicose veins and venous ulceration, as well as impaired reperfusion states such as those associated with reconstructive vascular surgery, thrombolysis and angioplasty. The invention also includes intermediates useful in the synthesis of these heterocyclic derivatives, processes for preparing the heterocyclic derivatives, pharmaceutical compositions containing such heterocyclic derivatives and methods for their use.

In U.S. Patent 4,499,082, of 12 February 1985, assigned to E. I. DuPont De Nemours and Company, there is disclosed a series of peptidyl boronic acid derivatives as reversible inhibitors of proteolytic enzymes, including HLE. It is well known that boronic acid derivatives, such as for example the corresponding esters, readily may be hydrolyzed under the <u>in vitro</u> and <u>in vivo</u> conditions in

which they are tested and used. In U.S. Patent 4,910,190, of 20 March 1990, assigned to ICI Americas Inc. (now ZENECA Inc.), there is disclosed a series of peptidoyl trifluoromethane ketone derivatives which are HLE inhibitors. Disclosed herein is a series of substituted 2-(2-oxo-1,2-dihydro-1-pyridyl)-N-[3,3-difluoro-1-(lower alkyl)-2-oxo-3-(boronic acid residue)propyl]acetamide derivatives, which unexpectedly possess inhibitory properties against HLE, which provides the basis for the present invention.

According to the invention there is provided a Compound of the invention which is a compound of formula I (formula set out, together with other formulae referred to by Roman numerals, following the Examples) wherein:

R^0 is (1-5C)alkyl;

R is hydrogen; or

R is an acyl group of formula A.X.CO- in which A.X-, taken together, is hydrogen, trifluoromethyl, 2,2,2-trifluoroethoxy, amino, methoxyamino, 2,2,2-trifluoroethylamino, RbRcN.O-, RaOCONH-, R^1SO_2NH-, RaOCO-, RbRcNCO- or RaCO-; or

R is an acyl group of formula A.X.CJ- in which

J is oxygen or sulfur;

X is a direct bond, imino, oxy or thio; and

A is as defined below or

A is tetrahydropyran-4-yl, 1-methylpiperid-4-yl, or 5-methyl-1,3-dioxacyclohex-5-ylmethyl; or

R is a sulfonyl group of formula D.W.SO_2- in which D.W-, taken together, is hydroxy, amino, di(lower alkyl)amino, 2,2,2-trifluoroethylamino, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl or trifluoromethyl; or

W is a direct bond, imino, carbonylimino, oxycarbonylimino or iminocarbonylimino; and

D is as defined below; or

R is a group G as defined below;

The group A, D or G is (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-3C)alkyl; aryl, aryl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)-alkyl wherein an aryl or heteroaryl moiety may bear one or more halogeno, nitro, methyl or trifluoromethyl groups and

further wherein the group A, D or G may bear one or more substituents selected from a group consisting of hydroxy, lower alkoxy, lower acyloxy, COORa, CH_2COORa, CONRbRc, $CH_2CONRbRc$, $COO(CH_2)_2NReRf$, cyano, SO_2R^1, $CONRdSO_2R^1$, NReRf, NRgCHO, $NRgCOR^2$, $NRgCOOR^2$, NRhCQNRiRj, $NRkSO_2R^3$, SO_2NRlRm, $SO_2NRnCOR^4$ and $P(O)(ORa)_2$ in which

Q is oxygen or sulfur;

Ra-Rn are independently hydrogen, benzyl or lower alkyl; or, independently, a group NRbRc, NReRf, NRiRj or NRlRm is a cyclic radical selected from a group consisting of 1-pyrrolidinyl, piperidino, morpholino or 1-piperazinyl which may bear a lower alkyl substituent at the 4-position; or, independently, a group NReRf is a cyclic radical selected from a group consisting of 2-pyrrolidinon-1-yl, succinimido, oxazolidin-2-on-3-yl, 2-benzoxazolinon-3-yl, phthalimido and cis-hexahydrophthalimido; and

R^1-R^4 are independently trifluoromethyl, (1-6C)alkyl, (3-6C)cycloalkyl, aryl or heteroaryl in which the aryl or heteroaryl may bear one or more substituents selected from a group consisting of lower alkyl, hydroxy, lower alkoxy, halogeno or trifluoromethyl;

Each of R^5 and R^6 is, independently, hydrogen or lower alkyl; or

One of R^5 and R^6 is hydrogen or methyl and the other of R^5 and R^6 is a radical of formula E.Y- in which

E is aryl or heteroaryl, which aryl or heteroaryl independently may bear one or more of the substituents defined for A, D or G or an aryl or heteroaryl moiety thereof;

Y is a direct bond, methylene, ethylene or trans-vinylene;

Q^1 and Q^2, which may be the same or different, is each hydroxy or OR^7, or when taken together from a moiety derived from a physiologically acceptable dihydroxy compound having at least two hydroxy groups separated by at least two connecting atoms in a chain or ring, said chain or ring comprising carbon atoms, and optionally, a heteroatom or atoms which can be O, S or N, wherein R^7 is (1-10C)alkyl, (3-10C)cycloalkyl, benzyl or phenyl in which benzyl or phenyl the ring may bear one or more halogeno, lower alkyl or lower alkoxy substituents; and

provided that no aliphatic carbon is bonded to more than one nitrogen or oxygen, except as part of a cyclic ketal or where the nitrogen bears a carbonyl group; or;

for a compound of formula I which is acidic or basic, a pharmaceutically acceptable salt thereof.

In this specification, the following definitions are used, unless otherwise described: Halogeno is fluoro, chloro, bromo or iodo. Alkyl, alkoxy, etc. denote both straight and branched groups; but reference to an individual radical such "propyl" embraces only the straight chain ("normal") radical, a branched chain isomer such as "isopropyl" being specifically referred to. Lower alkyl and lower alkoxy refer to radicals containing one to about four carbon atoms. Lower acyloxy refers to a radical containing one to about five carbon atoms. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propenylene, trimethylene or tetramethylene diradical thereto, as well as a stable N-oxide thereof.

It will be appreciated that, owing to the asymmetrically substituted carbon atom at the chiral center indicated by "*" in formula I, a compound of formula I may exist in, and be isolated in, optically active and racemic forms. If a compound of formula I contains an additional chiral element, such compound of formula I may exist in, and be isolated in, the form of a diastereomeric mixture or as a single diastereomer. It is to be understood that the present invention encompasses a compound of formula I as a mixture of diastereomers, as well as in the form of an individual diastereomer, and that the present invention encompasses a compound of formula I as a mixture of enantiomers, as well as in the form of an individual enantiomer. When R^0 is isopropyl, a compound of formula I may be viewed as a valyl (or "borovaline") derivative. In general, a

compound of formula I having the (S)-configuration at the chiral center indicated by "*", which corresponds to the L-alanyl configuration, is preferred. Accordingly, it may be preferred to use the compound of formula I in a form which is characterized as containing, for example, at least 95%, 98% or 99% enantiomeric excess (ee) of the (S)-form. However, owing to the interconvertability of the (S)-isomer and the (R)-isomer by the epimerization of the chiral center indicated by "*" in formula I, it may be preferred to utilize a compound of formula I as a mixture of the (S)- and (R)-isomers at the center indicated by "*" in formula I.

A compound of formula I may exhibit polymorphism. The compound may form solvates. A compound may exist in more than one tautomeric form. It is to be understood, therefore, that the present invention encompasses any racemic or optically-active form, any polymorphic form, any tautomer or any solvate, or any mixture thereof, which form possesses inhibitory properties against HLE, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form or by synthesis from optically-active starting materials) and how to determine the inhibitory properties against HLE by the standard tests described hereinafter.

derivatives

It is preferred that the radicals R^A, R^0, R, R^5 and R^6 not contain nor introduce an additional element of chirality into the molecule beyond the chiral center indicated by "*" in formula I; however, it may be preferred that the boron substituents Q^1 and Q^2 be chiral.

Particular values are listed below for radicals, substituents and ranges for illustration only and they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

A particular value for R^0 is ethyl or isopropyl.

A particular value for W is a direct bond or imino.

A particular value for G is (1-3C)alkyl, aryl(1-C)alkyl or heteroaryl(1-2C)alkyl which may bear one or more substituents as defined above for G or a part thereof.

A particular value of (1-6C)alkyl or (1-10C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, 3-methylbutyl, 1-ethylpropyl, hexyl or 4-methylpentyl. A particular value of (3-6C)cycloalkyl or (3-10C)cycloalkyl is cyclopropyl, cyclopentyl or cyclohexyl. A particular value for the (1-3C)alkyl portion of (3-6C)cycloalkyl-(1-3C)alkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl is methylene, ethylene or trimethylene. A particular value for aryl is phenyl, indenyl, indanyl or naphthyl. A particular value for heteroaryl is furyl, imidazolyl, tetrazolyl, pyridyl (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl or quinolinyl (or its N-oxide). A particular value for lower alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl. A particular value for lower acyloxy is acetoxy. A particular value for lower alkoxy is methoxy, ethoxy, propoxy, isoproxy or t-butoxy. A particular value for halogeno is bromo, chloro or fluoro.

A particular value for COORa is carboxy or methoxycarbonyl. A particular value for $NRgCOR^2$ is trifluoroacetylamino. A particular value of $CONRdSO_2R^1$ is N-phenylsulfonylcarbamoyl or N-(4-chlorophenylsulfonyl)carbamoyl. A particular value for A.X-, taken together, is tris(hydroxymethyl)methylamino, tris(acetoxymethyl)methylamino or 2,2-bis(hydroxymethyl)propoxy.

A more particular value for R^0 is isopropyl. A more particular value for J is oxygen. A more particular value for X is a direct bond, imino or oxy. A more particular value for A is methyl, ethyl, phenyl, benzyl, phenethyl, pyridyl, thienyl, 5-tetrazolyl, thiazolyl, pyridylmethyl, thenyl, 5-tetrazolylmethyl, 2-(pyridyl)ethyl, 2-(thienyl)ethyl or 2-(thiazolyl)ethyl wherein the phenyl or heteroaryl group may bear one or two halogeno or methyl groups and further wherein the group A may bear a substituent selected from hydroxy, methoxy, t-butoxy, acetoxy, pivaloyloxy, carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, dimethylcarbamoyl, 2-(dimethylamino)ethoxycarbonyl, cyano, methylsulfonyl, phenylsulfonyl, N-methylsulfonylcarbamoyl, N-phenylsulfonylcarbamoyl, amino, dimethylamino, oxazolidin-2-on-3-yl, acetylamino, trifluoroacetylamino, ureido, methylsulfonyl, sulfamoyl, dimethylphosphoryl or diethylphosphoryl. A more particular value for

D is methyl, ethyl, isopropyl, tert-butyl, cyclohexyl, phenyl, benzyl, phenethyl, pyridyl, thienyl, 5-tetrazolyl, thiazolyl, quinolinyl, pyridylmethyl, thenyl, 5-tetrazolylmethyl, 2-(pyridyl)ethyl, 2-(thienyl)ethyl or 2-(thiazolyl)ethyl wherein the phenyl or heteroaryl group may bear one or two halogeno or methyl groups and further wherein the group D may bear a substituent selected from hydroxy, methoxy, t-butoxy, acetoxy, pivaloyloxy, carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, dimethylcarbamoyl, 2-(dimethylamino)ethoxycarbonyl, cyano, methylsulfonyl, phenylsulfonyl, N-methylsulfonylcarbamoyl, N-phenylsulfonylcarbamoyl, N-(4-chlorophenylsulfonyl)carbamoyl, methylsulfonylamino, amino, dimethylamino, oxazolidin-2-on-3-yl, acetylamino, trifluoroacetylamino, ureido, methylsulfonyl, sulfamoyl, dimethylphosphoryl or diethylphosphoryl. A more particular value for G is methyl, ethyl, benzyl, phenethyl, pyridyl, pyridylmethyl, thenyl, 5-tetrazolylmethyl, or 2-(pyridyl)ethyl, wherein an alkyl carbon may bear an oxo group and wherein the phenyl or heteroaryl group may bear one or two halogeno or methyl groups and further wherein the group G may bear a substituent selected from hydroxy, methoxy, acetoxy, carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, dimethylcarbamoyl, phenylcarbamoyl, pyridylcarbamoyl, methylsulfonylamino, amino, dimethylamino, acetylamino, nicotinoylamino, or trifluoroacetylamino.

A particular value for R is, for example, hydrogen, trifluoroacetyl, hydroxyoxalyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, 4-fluorophenoxycarbonyl, 4-bromophenoxycarbonyl, 4-methoxyphenoxycarbonyl, benzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-pyridylmethoxycarbonyl, 3-methylpyrid-4-ylmethoxycarbonyl, 2,6-dimethylpyrid-4-ylmethoxy-carbonyl, 2-pyridylmethoxycarbonyl, 6-methylpyrid-2-ylmethoxycarbonyl, 2-dimethylaminoethoxycarbonyl, acetyl, carbamoylmethylaminocarbonyl, 4-(N-phenylsulfonylcarbamoyl)phenylacetyl, sulfo, aminosulfonyl, dimethylaminosulfonyl, trifluoromethylsulfonyl, methylsulfonyl (which may bear a methoxycarbonyl, carboxy or ethylsulfonyl substituent), methylaminosulfonyl, isopropylaminosulfonyl, butylsulfonyl, butylaminosulfonyl, tert-butylaminosulfonyl, cyclohexylaminosulfonyl,

phenylsulfonyl (in which the phenyl may bear a chloro, nitro, amino, acetylamino, trifluoroacetylamino, methoxy, carboxy, N-(4-chlorophenylsulfonyl)carbamoyl, or methylsulfonylamino substituent at the 3- or 4-position), anilino, pyridylsulfonyl, quinolinylsulfonyl, benzylsulfonyl (in which the phenyl ring may bear a nitro or amino substituent at the 3- or 4-position), pyridylmethylsulfonyl, 2-(pyridyl)ethylsulfonyl, benzylaminosulfonyl, methyl, ethyl, benzyl, phenethyl or pyridylmethyl.

A particular value for Q^1 and Q^2 is, for example, hydroxy, methoxy, ethoxy or isopropoxy; or, when Q^1 and Q^2 are taken together, a particular value is, for example, the residue derived from 2,3-butanediol, 2,3-dimethyl-2,3-butanediol, 1,3-propanediol, diethanolamine, catechol, (1R,2R,3S,5R)-(-)- or (1S,2S,3R,5S)-(+)-pinanediol, or 2,5-dimethylhexan-3,4-diol. A more particular value for Q^1 or Q^2 is, for example, methoxy or ethoxy; or, when Q^1 and Q^2 are taken together, the residue derived from 2,3-dimethylbutane-2,3-diol or 1,3-propanediol.

One particular group of compounds of formula I is one in which Q^1, Q^2, R^0 and R have any of the values defined above, R^5 is hydrogen and R^6 is hydrogen.

Another particular group of compounds of formula I is one in which Q^1, Q^2, R^0 and R have any of the values defined above, R^5 is benzyl, the phenyl ring of which may bear a 3-fluoro, 4-fluoro, 4-trifluoromethyl, 4-methoxycarbonyl, 3-acetoxy, 3-hydroxy, 3-pivaloyloxy, 4-hydroxy, 4-pivaloyloxy, 3-trifluoroacetylamino or 3-amino substituent, and R^6 is hydrogen.

A further particular group of compounds of formula I is one in which Q^1, Q^2, R^0 and R have any of the values defined above, R^5 is hydrogen, and R^6 is 2-furyl, 2-thienyl, 3-pyridyl or phenyl in which the phenyl may bear one or two halogeno, trifluoromethyl, methyl, hydroxy, methoxy, tert-butoxy, methoxycarbonyl or carboxy substituents; and, more particularly, R^6 is phenyl, 4-fluorophenyl or 2-thienyl.

Specific compounds of formula I are described in the accompanying Examples. Of these, compounds of particular interest

along with their pharmaceutically acceptable salts, include those described in Examples 3 and 4.

A pharmaceutically acceptable salt of an acidic compound of formula I is one made with a base which affords a pharmaceutically acceptable cation, which includes alkalai metal salts (especially lithium, sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from appropriate organic bases such as triethylamine, morpholine, piperidine and triethanol amine. A pharmaceutically acceptable salt of a basic compound of formula I includes an acid-addition salt made with an acid which provides a pharmaceutically acceptable anion, including for example, a strong acid such as hydrochloric, sulfuric or phosphoric acid.

It will be noted that other boronic acid derivatives have been disclosed as inhibitors of serine proteases in which the boron substituents corresponding to Q^1 and Q^2 are acyl, amino or carbamoyl radicals (see, for example, European Patent Application, Publication Number 471 651 A2), and that analogous boronic derivatives corresponding to a compound of formula I are also included as an aspect of the present invention.

A compound of formula I may be made by processes which include processes known in the chemical art for the production of structurally analogous heterocyclic and peptidic compounds. Such processes and intermediates for the manufacture of a compound of formula I as defined above are provided as further features of the invention and are illustrated by the following procedures in which the meanings of generic radicals are as defined above:

(A) Coupling a corresponding acid of formula IIa, or an activated derivative thereof, with a corresponding amine of formula IIb, using a conventional coupling method. An amine of compound IIb conveniently may be used as an acid addition salt and converted into its free base <u>in situ</u>. Conventional coupling methods include coupling with a water soluble carbodimide (Coupling Method A) and the mixed anhydride method (Coupling Method B) as described in Example 1.

(B) For a compound of formula I which contains an N-H residue, removal by using a conventional method of the nitrogen protecting group of a corresponding compound bearing a conventional

nitrogen protecting group to afford the compound of formula I which contains an amino N-H residue, particularly for a compound of formula I in which R is hydrogen, removal of a group from a corresponding compound of formula I, for example as described in Example 3, or for a compound of formula I in which R has a value of G, the removal of an activating/protecting group Rx from a corresponding compound of formula Vb. Rx is a group which protects and activates a primary amino group for substitution, such as for example benzyloxycarbonyl or trifluoroacetyl. Conventional methods include, for example, removal of a benzyloxycarbonyl group by hydrogenolysis, removal of a benzyloxycarbonyl or tert-butoxycarbonyl group by treatment with a strong acid, for example with trifluoromethanesulfonic acid in an inert solvent such as dichloromethane, or basic hydrolysis of a trifluoroacetyl group.

(C) For a compound of formula I wherein R is an acyl group, acylation of a corresponding amine of formula I wherein R is hydrogen. Convenient methods include, for example, when J is oxygen, the use of an activated carboxylic acid derivative, such as an acid halide, the use of a carboxylic acid and a coupling reagent, the use of an isocyanate for a compound wherein X is imino, and the use of a diactivated carbonic acid derivative, for example, carbonyldiimidazole, phosgene, diphosgene (trichloromethyl chloroformate) or triphosgene (bis(trichloromethyl) carbonate) with an alcohol of formula A.OH, a thiol of formula A.SH or an amine of formula $A.NH_2$ and a base, such as triethylamine or, when J is sulfur, the use of an activated thiocarboxylic acid derivative, such as a thioyl chloride or a lower alkyl ester of a dithioic acid, the use of a thioic acid and a coupling reagent, the use of an isothiocyanate for a compound wherein X is imino, and the use of a diactivated thiocarbonic acid derivative, for example, dimethyl trithiocarbonate, with an alcohol of formula A.OH, a thiol of formula A.SH or an amine of formula $A.NH_2$.

(D) For a compound of formula I wherein R is a sulfonyl group, sulfonylation of a corresponding amine of formula I wherein R is hydrogen with a corresponding sulfonic acid of formula $D.W.SO_2.OH$,

or an activated derivative thereof, such as an acid halide, particularly a sulfonyl (or sulfamoyl) chloride of formula $D.W.SO_2.Cl$. The sulfonylation is conveniently carried out in an inert solvent or diluent, such as dichloromethane, tetrahydrofuran or toluene, at about ambient temperature, using an organic base such as, for example, triethylamine or pyridine, or an inorganic base, such as sodium or potassium carbonate, as an acid acceptor. If a sulfonyl chloride is not commercially available, it may be obtained by a conventional method.

(E) For a compound of formula I in which R is a group G, substitution of the group L of a corresponding compound of formula G-L, wherein L is a conventional leaving group, such as for example halogeno, methylsulfonyloxy, trifluoromethylsulfonyloxy or diazonium, with a corresponding amine of formula I wherein R is hydrogen, optionally using a conventional catalyst.

(F) For a compound of formula I which bears a hydroxy substituent on an aryl or heteroaryl group, cleaving the alkyl ether or acyloxy ester of a corresponding compound of formula I which bears a lower alkoxy or lower acyloxy substituent on an aryl or heteroaryl group. Convenient methods include, for example, the cleavage of a methoxy group using boron tribromide or pyridinium chloride and the cleavage of a t-butoxy group using trifluoroacetic acid for an alkyl ether, and the acidic or alkaline hydrolysis of an acyloxy group.

(G) For a compound of formula I which bears a group of formula COORa in which Ra is hydrogen (a carboxy group), decomposing the ester group of a corresponding ester made with a conveniently removed acid protecting group, for example a corresponding compound of formula I in which Ra is not hydrogen. The decomposition may be carried out using any one of the variety of procedures well known in organic chemistry, for example basic hydrolysis using lithium or sodium hydroxide, or by hydrogenolysis of a benzyl ester.

(H) For a compound of formula I bearing a moiety of formula COORa, CH_2COORa, CONRbRc, $CH_2CONRbRc$, $COO(CH_2)_2NReRf$ or $CONRdSO_2R^1$, acylation of a corresponding compound of formula HORa, HNRbRc, $HO(CH2)_2NReRf$ or $HNRdSO_2R^1$ with a corresponding acid of formula I

bearing a moiety of formula COORa in which Ra is hydrogen, or an activated derivative thereof;

(I) For a compound of formula I bearing a lower acyloxy group or a group of formula NRgCHO, $NRgCOR^2$, $NRgCOOR^2$, NRhCQNRiRj or $NRkSO_2R^3$, acylation or sulfonylation of a corresponding compound of formula I bearing a hydroxy group or an amino group of formula NHRg, NHRh or NHRk (i.e. an amino group of formula NReRf is which Re is hydrogen and Rf is Rg, Rh or Rk) with an activated derivative of a corresponding acid of formula HOCHO, $HOCOR^2$, $HOCOOR^2$, HOCQNRiRj (including an isocyanate or isothiocyanate) or $HOSO_2R^3$, respectively, using a conventional method;

(J) For a compound of formula I which bears a heteroaryl N-oxide group, oxidation of a corresponding compound of formula I which bears a heteroaryl group using a conventional oxidant, such as for example dioxirane in acetone.

(K) For a compound of formula I which bears a primary amino group, reduction of a corresponding compound bearing a nitro group using a conventional reducing method, such as for example, hydrogenation over a palladium catalyst, or reduction with tin(II) chloride.

(L) For a compound of formula I in which Q^1 and/or Q^2 is hydroxy, conversion of the corresponding group Q^1 and/or Q^2 of a compound of formula I in which Q^1 and/or Q^2 is not hydroxy into a hydroxy group by a conventinal method. Conventional method include, for example, hydrogenolysis of a group in which Q^1 and/or Q^2 is benzyl or hydrolysis of a group Q^1 and/or Q^2 with aqueous acid.

Whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of an acidic or basic compound of formula I is required, it may be obtained by reacting the acidic or basic form of such a compound of formula I with a base or acid affording a physiologically acceptable counterion or by any other conventional procedure.

If not commercially available, the necessary starting materials for the above procedures may be made by procedures which are selected from standard techniques of heterocyclic chemistry and peptide chemistry, techniques which are analogous to the synthesis of

known, structurally similar compounds, and techniques which are analogous to the above described procedures or the procedures described in the Examples. For uniformity and clarity, compounds herein are represented as the 2-pyridone, rather than the 2-hydroxypyridine, tautomers.

As will be clear to one skilled in the art, a variety of sequences is available for preparation of the starting materials. According to one of the available routes, a key intermediate pyrid-2-one-3-carboxylic acid of formula III may be prepared as shown in Scheme I (set out, together with other Schemes, following Examples). In the Schemes, CBZ represents a benzyloxycarbonyl group.

In general, in a formal sense, a ketone of formula $R^5.CH_2.CO.R^6$ may be formylated, then cyclized with cyanoacetamide to afford a pyrid-2-one-3-carbonitrile of formula IV. Thus, (Cyclization Method A) the ketone may be formylated with dimethylformamide dimethyl acetal in acetonitrile, then the isolated intermediate cyclized with cyanoacetamide, using sodium methoxide in dimethylformamide. Alternatively, (Cyclization Method B) the ketone may be formylated using sodium methoxide and ethyl formate in tetrahydrofuran or ether, distilling the solvent, dissolving the resulting salt in water, adding acetic acid to pH 9, and heating with cyanoacetamide at 90 °C to achieve the cyclization. As a further varation, (Cyclization Method C) the salt resulting from formylation with sodium methoxide and ethyl formate, followed by removal of the solvent, may be cyclized with cyanoacetamide by heating an aqueous solution with piperidine acetate as a catalyst. Where more than one product is possible from the cyclization reaction, the product selectivity may be controlled by the cyclization (and formylation) method chosen. For example, cyclization of phenylacetone by Cyclization Method A affords 6-methyl-5-phenyl-pyrid-2-one-3-carbonitrile; but cyclization of phenylacetone by Cyclization Method C affords 6-benzylpyrid-2-one-3-carbonitrile. Hydrolysis of the cyano group of a compound of formula IV, for example by heating with 48% hydrobromic acid in acetic acid (Hydrolysis Method A) or with sodium hydroxide solution in a pressure vessel (Hydrolysis Method B) affords a corresponding carboxy derivative of formula III. For a compound in which R^6 is E.Y- and Y

is ethylene or trans-vinylene, it may be preferred to proceed via an alternative route to an acid of formula III. Thus, cyclization of a ketone of formula $R^5.CH_2.CO.CH_3$ affords a 6-methyl pyridone derivative of formula IVa, for example, cyclizing acetone by Cyclization Method C. Bis-metallation, followed by alkylation with a reagent of, for example, formula $E.CH_2.Br$ affords a corresponding nitrile of formula IV in which Y is ethylene. Alternatively, bis-metallation of a 6-methyl pyridone of formula IVa, followed by condensation with an aldehyde of formula E.CHO, affords a pyrid-2-one-3-carbonitrile of formula IVb which may be converted by acid hydrolysis and dehydration into a corresponding pyride-2-one-3-carboxylic acid of formula III in which Y is trans-vinylene.

An acid of formula III may be converted into a corresponding isocyanate of formula VI by a conventional method, for example by using triethylamine and diphenylphosphoryl azide in an inert solvent, for example dioxane or toluene, at an elevated temperature. Conveniently, the isocyanate is not isolated, but is converted into a benzyl urethane of formula VII as also is shown in Scheme I. It will be clear to one skilled in the art that, in general, treatment of an isocyanate of formula VI with a selected alcohol or amine of formula A.X.H in which X is oxy or imino will provide a corresponding product of formula VIIa in which X is oxy or imino, and that the product of formula VIIa may be carried forward to an acetic acid of formula IIa using one of the routes outlined below. (An isocyanate of formula VI may undergo intramolecular cyclization to the oxygen at the pyridone 2-position, thereby forming a corresponding cyclic carbamate, which carbamate similarly may afford a corresponding compound of formula VII or VIIa.)

Elaboration of a substituted amino pyridone of formula VII or VIIa into a corresponding intermediate acetic acid of formula IIa or a corresponding intermediate amine of formula Vb may be carried out as outlined. Thus, a pyridone of formula VII may be alkylated, for example with ethyl or t-butyl iodoacetate using sodium hydride in dimethylformamide, to afford a corresponding ester of formula XI, wherein Rq is a conveniently removable acid protecting group, for example ethyl or t-butyl. (The corresponding 2-alkoxypyridine

resulting from O-alkylation is also obtained. When R^6 is subject to hindered rotation, for example when R^5 is methyl and R^6 is phenyl, or, for example, when R^5 is hydrogen and R^6 is 2-chlorophenyl, the ratio of N-alkylated product to O-alkylated product is increased.) Removal of the acid protecting group of an ester of formula XI by a conventional method, for example by base catalyzed hydrolysis or by acid catalyzed elimination, affords a corresponding acid of formula XII. An acid of formula XII is an acid of formula IIa in which R is benzyloxycarbonyl.

An alternative route for the preparation of an intermediate acid of formula XII, beginning with a ketone of formula $R^5.CH_2.CO.R^6$ and involving a novel pyridone synthesis, which may be a preferred route, is described in Example 1, parts a.-f., for the conversion of acetophenone into 3-benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridylacetic acid.

Coupling an acid of formula XII with an amine of formula IIb, as described in process (A) above, affords a corresponding compound of formula I wherein R is benzyloxycarbonyl. Removal of the nitrogen protecting group of a compound of formula I wherein R is benzyloxycarbonyl by hydrogenolysis, for example as described in Example 3, affords a corresponding amine of formula I wherein R is hydrogen. (See Scheme II.)

A preferred method for introducing the substituent R when it is a group G, particularly when it is an alkyl or substituted alkyl group, is by the use of a corresponding compound in which the pyridone 3-amino substituent bears an activating/protecting group of formula Rx, for example, benzyloxycarbonyl or trifluoroacetyl. Thus, acylation of a compound of formula I wherein R is hydrogen with trifluoroacetic anhydride affords a corresponding compound of formula Va in which Rx is trifluoroacetyl, which compound also may be prepared by an alternative order of steps via the corresponding compound of formula IX. It will be noted that a compound of formula VIIIb is, itself, a corresponding compound of formula Va in which Rx is benzyloxycarbonyl. Also, each of a compound of formula Va in which Rx is benzyloxycarbonyl or trifluoroacetyl is also a compound of formula I in which R is an acyl group. Alkylation, using a corresponding

reagent of formula G.L in which G is alkyl or substituted alkyl, then provides a corresponding intermediate of formula Vb.

Synthesis routes involving a cross coupling reaction to introduce a substituent R^5 into intermediate compounds are outlined in Scheme III. These routes may be preferred when R^5 has the value E.Y- and Y is methylene, ethylene or trans-vinylene. Thus, a pyridone of formula VII in which R^5 is hydrogen may be converted into a corresponding 5-iodo pyridone of formula XXI by treatment with an iodinating agent, for example N-iodosuccinimide. An appropriate halide, for example a bromide of formula $E.CH_2.Br$, may be converted into a corresponding organozinc reagent, for example $E.CH_2.Zn.Br$, by treatment with zinc dust in tetrahydrofuran, and cross-coupled with an iodide of formula XXI using a palladium catalyst, such as dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) to afford a corresponding compound of formula VII in which R^5 is E.Y- and Y is methylene. A similar cross coupling utilizing a bromide of formula E.Y.Br in which Y is trans-vinylene may be useful to convert an iodide of formula XXI into a corresponding compound of formula VII in which R^5 is E.Y- and Y is trans-vinylene. At a convenient point in a synthesis, a compound in which R^5 is E.Y- and Y is trans-vinylene may be hydrogenated to afford a corresponding compound in which R^5 is E.Y- and Y is ethylene.

Alternatively, using a method described above, an iodide of formula XXI may be converted into a corresponding iodide of formula XXII which may be further cross coupled as described above to provide a corresponding compound of formula XI.

Alternative synthesis routes in which a 3-nitro pyridone serves as a precursor to a 3-amino pyridone are outlined in Scheme IV. They may be particularly useful when the 3-nitro derivative is readily available, such as when R^5 and R^6 are hydrogen as described in Example 2. Alternatively, beginning with a ketone of formula $R^5.CH_2.CO.R^6$, the corresponding 3-nitropyridone may be prepared in a manner analogous to Cyclization Method A by heating a dimethylformamide solution of the ammonium salt of nitroacetamide (prepared according to J. Org. Chem. (1958), 23, 113-114) with the product isolated from treatment of the ketone with dimethylformamide dimethyl acetal in acetonitrile. Direct reduction of the nitro group,

followed by substitution (particularly acylation or sulfonylation) of the amine obtained, provides a pyridone of formula VIIb, which may be converted into a corresponding intermediate of formula IIa or formula Vb using a route similar to one outlined above for a compound of formula VII. Using a different order of steps, the 3-nitro pyridone may be alkylated first to provide an ester of formula XXIV. The ester of formula XXIV may be converted into the corresponding acid of formula XXV. The acid of formula XXV also may be obtained by allylation of the starting 3-nitro pyridone, followed by oxidative cleavage of the 1-allyl group using potassium permanganate. By coupling with the appropriate amine of formula IIb, an acid of formula XXV may be converted into a nitro derivative of formula XXVIII. Reduction of the nitro group of a nitro derivative of formula XXVIII affords an amine of formula I in which R is hydrogen. An analogous route from a nitro compound of formula XXIV involves first reducing the nitro group to afford a corresponding amino compound of formula XXIX. Sustitution of the amino group of a compound of formula XXIX using a method similar to one described above affords a compound of formula XIb, which may be further converted into a corresponding compound of formula IIa using a similar method to one described above for a compound of formula XI. By using analogous methods to those described above, a compound of formula XI prepared by one of the methods described above can also be converted into a corresponding ester of formula XIb, and further into a corresponding compound of formula IIa.

The preparation of intermediate amines of formula IIb is well known in the art. The preparation of compounds of formula IIb in which Q^1 and Q^2 together form the residue of a dihydroxy compound is particularly described in U.S. Patent 4,537,773 of 27 August 1985.

It may be desired optionally to use a protecting group during all or portions of the above described processes; the protecting group then may be removed when the final compound or a required starting material is to be formed. As will be clear to one skilled in the art, the order of steps in the sequences leading to the starting materials and products of the invention may be altered if

appropriate considerations relative to coupling methods, racemization, deprotection methods, etc. are followed.

The utility of a compound of the invention or a pharmaceutically acceptable salt thereof (hereinafter, collectively referred to as a "Compound") may be demonstrated by standard tests and clinical studies, including those described below.

Inhibition Measurements:

The potency of a Compound to act as an inhibitor of human leukocyte elastase (HLE) on the low molecular weight peptide substrate methoxy-succinyl-alanyl-alanyl-prolyl-valine-p-nitroanilide is determined as described in U.S. Patent 4,910,190. The potency of an inhibitor is evaluated by obtaining a kinetic determination of the dissociation constant, K_i, of the complex formed from the interaction of the inhibitor with HLE. If a Compound is found to be a "slow-binding" inhibitor of HLE, special methods of analysis to accurately determine K_i values for the inhibition of HLE are carried out as described in U.S. Patent 4,910,190. In general, the K_i values for Compounds of the invention which were tested are generally on the order of 10^{-7} M or much less.

Acute Lung Injury Model:

Animal models of emphysema include intratracheal (i.t.) administration of an elastolytic protease to cause a slowly progressive, destructive lesion of the lung. These lesions are normally evaluated a few weeks to a few months after the initial insult. However, these proteases also induce a lesion that is evident in the first few hours. The early lesion is first hemorrhagic, progresses to an inflammatory lesion by the end of the first 24 hours and resolves in the first week post insult. To take advantage of this early lesion, the following model (described in Williams, et al., American Review of Respiratory Diseases (1991), 144, 875-838) was used.

Hamsters are first lightly anesthetized with Brevital. Phosphate buffered saline (PBS) pH 7.4, either alone or containing human leukocyte elastase (HLE), is then administered directly into the trachea. Twenty-four hours later the animals are killed and the lungs removed and carefully trimmed of extraneous tissue. Following determination of wet lung weight, the lungs are lavaged with PBS and

total lavagable red and white cells recovered are determined. The values for wet lung weights, total lavagable red cells and total lavagable white cells are elevated in a dose-dependent manner following administration of HLE. Compounds that are effective elastase inhibitors can prevent or diminish the severity of the enzyme-induced lesion resulting in lower wet lung weight and reduced values for total lavagable cells, both red and white, relative to administration of HLE alone. Compounds can be evaluated by administering them intratracheally as solutions or suspensions in PBS, either with or at various times prior to the HLE challenge (400 µg), or by dosing them intravenously or orally as solutions at various times prior to the HLE challenge (100 µg) to determine their utility in preventing an HLE lesion. A solution of a Compound is conveniently prepared using 10% polyethylene glycol 400/PBS or 10% polyethylene glycol 400/water. For a Compound which is acidic or basic, base (e.g. sodium hydroxide solution) or acid (e.g. hydrochloric acid) may be added as indicated to achieve solution. Compounds of this invention produced statistically significant reductions in wet lung weight and total lavagable cells relative to HLE alone.

Acute Hemorrhagic Assay:

This assay relies on monitoring only the amount of hemorrhage in the lung following intratracheal administration of human neutrophil elastase (HNE). Hemorrhage is quantified by disrupting erythrocytes recovered in lung lavage fluid and comparing that to dilutions of whole hamster blood. The screening protocol, similar to that described in Fletcher et al., American Review of Respiratory Disease (1990), 141, 672-677, is as follows. Compounds demonstrated to be HNE inhibitors in vitro are conveniently prepared for dosing as described above for the Acute Lung Injury Model. The compounds are then dosed by mouth to male Syrian hamsters at a fixed time, such as 30 or 90 min, prior to intratracheal administration of 50 µg/animal of HNE in 300 µL phosphate buffered saline (PBS) pH 7.4. Four hours after enzyme administration, the animals are killed with an overdose of pentobarbital sodium, the thorax opened and the lungs and trachea removed. The excised lungs are lavaged with three changes of 2 mL normal saline via a tracheal cannula. The recovered lavages are

pooled, the volumes (about 5 mL) are recorded and the lavages stored at 4 °C until assayed. For calculation of the amount of blood in each sample, the thawed lavages and a sample of whole hamster blood are sonicated to disrupt erythrocytes and appropriately diluted into individual wells of a 96-well microtiter plate. The optical densities (OD) of the disrupted lavages and blood samples are determined at 405 nm. The (µL blood equivalents) / (mL lavage) are determined by comparing the OD of the test samples with the OD of the standard curve prepared from whole hamster blood. The total µL equivalents of blood recovered is determined by multiplying recovered lavage volume by the (µL blood equivalents) / (mL lavage) for each sample. Results are reported as % inhibition of hemorrhage with respect to PBS treated controls when the test compound is given at a specified dose and time prior to administration of HNE.

No overt toxicity was observed when Compounds of the invention were administered in the above in vivo tests.

It will be appreciated that the implications of a Compound's activity in the Acute Lung Injury Model or Acute Hemorrhagic Assay are not limited to emphysema, but, rather, that the test provides evidence of general in vivo inhibition of HLE.

Compounds of the present invention which were tested exhibited activity in at least one of the tests described above under Inhibition Measurement, Acute Lung Injury Model and Acute Hemorrhagic Assay. As noted above, a compound of formula I in which Q^1 and/or Q^2 is not hydroxy may be converted into a corresponding compound of formula Q^1 and/or Q^2 is hydroxy under the condition of an in vivo or in vitro test. Accordingly, in general the in vitro inhibition measurements were done at intervals, such as overnight, which ensured complete hydrolysis of the boronate esters. It should be noted that, as would be expected in comparison of in vitro and in vivo results, there was not always a direct correlation between the activities of the compounds measured as K_i values in the Inhibition Measurement test and the reduced values for total lavagable cells and wet lung weights relative to the administration of HLE alone obtained in the Acute Lung Injury Model test or inhibition of hemorrhage in the Acute Hemorragic Assay.

According to a further feature of the invention, there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of a Compound and a pharmaceutically acceptable diluent or carrier. As noted above, another feature of the invention is a method of using a Compound of the invention in the treatment of a disease or condition in a mammal, especially a human, in which HLE is implicated.

A Compound of the present invention may be administered to a warm-blooded animal, particularly a human, in need thereof for treatment of a disease in which HLE is implicated, in the form of a conventional pharmaceutical composition, for example as generally disclosed in U.S. Patent 4,910,190. The preferred mode of administration may be via a powdered or liquid aerosol. In a powdered aerosol, a Compound of the invention may be administered in the same manner as cromolyn sodium via a 'Spinhaler' (a trademark) turbo-inhaler device obtained from Fisons Corp. of Bedford, Massachusets at a rate of about 0.1 to 50 mg per capsule, 1 to 8 capsules being administered daily for an average human. Each capsule to be used in the turbo-inhaler contains the required amount of a Compound of the invention with the remainder of the 20 mg capsule being a pharmaceutically acceptable carrier such as lactose. In a liquid aerosol, a Compound of the invention may be administered using a nebulizer such as, for example, a 'Retec' (trademark) nebulizer, in which the solution is nebulized with compressed air. The aerosol may be administered, for example, at the rate of one to about eight times per day as follows: A nebulizer is filled with a solution of a Compound, for example 3.5 mL of solution containing 10 mg/mL; the solution in the nebulizer is nebulized with compressed air; and the patient breathes normally (tidal volume) for eight minutes with the nebulizer in his mouth.

Alternatively, the mode of adminstration may be oral or parenteral, including subcutaneous deposit by means of an osmotic pump. A compound of the invention may be conventionally formulated in an oral or parenteral dosage form by compounding about 10 to 250 mg per unit of dosage with conventional vehicle, excipient, binder, preservative, stabilizer, flavor or the like as called for by accepted

pharmaceutical practice, e.g. as described in U.S. Patent 3,755,340. For parenteral administration, a 1 to 10 mL intravenous, intramuscular or subcutaneous injection would be given containing about 0.02 mg to 10 mg/kg of body weight of a compound of the invention 3 or 4 times daily. The injection would contain a compound of the invention in an aqueous isotonic sterile solution or suspension optionally with a preservative such as phenol or a solubilizing agent such as ethylenediaminetetraacetic acid (EDTA).

For parenteral administration or use in an aerosol, an 10 mg/mL aqueous formulation of an acidic Compound may be prepared, for example by dissolving the Compound (10 mg), dibasic sodium phosphate heptahydrate, USP (11.97 mg), monobasic sodium phosphate, USP (0.74 mg), sodium chloride, USP (4.50 mg) and sufficient 1 N sodium hydroxide solution or 0.05 M monobasic sodium phosphate solution to achieve pH 7.0-7.5 in sufficient water for injection, USP to afford 1.0 mL (1.01 g), followed by aseptic filtration, and sterile storage using standard procedures.

In general, a Compound of the invention will be administered to humans at a daily dose in the range of, for example, 5 to 100 mg of the Compound by aerosol or 50 to 1000 mg intravenously, or a combination of the two. However, it readily will be understood that it may be necessary to vary the dose of the Compound adminstered in accordance with well known medical practice to take account of the nature and severity of the disease under treatment, concurrent therapy, and the age, weight and sex of the patient receiving treatment. It similarly will be understood that generally equivalent amounts of a pharmaceutically acceptable salt of the Compound also may be used. Protocols for the administration of an HLE inhibitor and evaluation of the patients are described in the European Patent Applications with Publication Numbers 458535, 458536, 458537, and 463811 for the treatment or prevention of cystic fibrosis, ARDS, bronchitis, and hemorrhage associated with acute non-lymphocytic leukemia or its therapy, respectively; and a Compound of the invention may be used similarly for the treatment of those diseases and conditions either alone or in combination with another therapeutic agent customarily indicated for the treatment of the particular

condition. For therapeutic or prophylactic treatment of a vascular disease or related condition in a mammal in which neutrophils are involved or implicated, a Compound of the invention may conveniently be administered by a parenteral route, either alone or simultaneously or sequentially with other therapeutically active agents customarily administered for the condition.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C;

(ii) organic solutions were dried over anhydrous sodium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals; 4.5-30 mm Hg) with a bath temperature of up to 60 °C;

(iii) chromatography means 'flash chromatography' (method of Still) carried out on Merck Kieselgel (Art 9385 from E. Merck, Darmstadt, Germany); if "acidic silica gel" is indicated, material custom prepared by J. T. Baker Chemical Co., Phillipsburg, NJ, USA, and having a pH of about 6 when slurried in water was used; reversed phase chromatography means flash chromatography over octadecylsilane (ODS) coated support having a particle diameter of 32-74 μ, know as "PREP-40-ODS" (Art 731740-100 from Bodman Chemicals, Aston, PA, USA); thin layer chromatography (TLC) was carried out on 0.25 mm silica gel GHLF plates (Art 21521 from Analtech, Newark, DE, USA); reversed phase-TLC (RP-TLC) was carried out Whatman $MKC_{18}F$ plates (Art 4803-110 from Bodman Chemicals);

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) melting points are uncorrected and (dec) indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(vi) final products had satisfactory nuclear magnetic resonance (NMR) spectra;

(vii) yields are given for illustration only and are not

necessarily those which may be obtained by diligent process development; preparations were repeated if more material was required;

(viii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 250 MHz using DMSO-d_6 as solvent; conventional abbreviations for signal shape are used; for AB spectra the directly observed shifts are reported;

(ix) chemical symbols have their usual meanings; SI units and symbols are used;

(x) reduced pressures are given as absolute pressures in pascals (Pa); elevated pressures are given as gauge pressures in bars;

(xi) solvent ratios are given in volume:volume (v/v) terms; and

(xii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionizaton mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI) or fast atom bombardment (FAB); generally, only peaks which indicate the parent mass are reported.

EXAMPLE 1. 2-(3-Benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-[2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidine-2-yl)-propyl]acetamide.

To a solution of 3-benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydropyridylacetic acid (0.25 g), 4-methylmorpholine (0.15 mL), 1-hydroxybenzotriazole hydrate (0.19 g) and 2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidin-2-yl)propylammonium trifluoroacetate (0.26 g) in tetrahydrofuran (6 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.14 g). The mixture was stirred overnight, diluted with ethyl acetate, and washed with water. The organic layer was dried and evaporated to give an oil/foam which was purified by chromatography, with chloroform:-methanol (50:1) as the eluent, to give an oil, which was dried overnight under vacuum to give the title compound (0.28 g) as a yellow foam; TLC: R_f=0.64, methanol:chloroform (1:20); NMR: 0.82-0.86 (m,6), 1.16 (s,12), 2.60 (t,1), 4.43 (broad s, 2), 5.19 (s,2), 6.22 (d,1), 7.33-7.50 (m,10), 7.91 (d,1), 8.25 (d,1), 8.52 (s,1); MS: m/z=560(M+1). Analysis for $C_{31}H_{38}BN_3O_6 \cdot 0.4\ H_2O$: Calculated: C, 65.71; H, 6.90; N, 7.42; Found: C, 65.62; H, 7.17; N, 7.07.

Henceforth this procedure will be referred to as Coupling Method A.

Alternatively, the title compound may be prepared by the following procedure:

A solution of 3-benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydropyridylacetic acid (0.50 g) and 4-methylmorpholine (0.16 mL) in tetrahydrofuran (7 mL) was cooled to -25 °C. The dropwise addition of isobutyl chloroformate (0.19 mL) over 3.5 minutes caused formation of a thick, pale yellow suspension. The mixture was stirred at a bath temperature of -25 to -20 °C and 4-methylmorpholine (0.16 mL), and 2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidin-2-yl)propylammonium trifluoroacetate (0.43 g) were added. Stirring was continued at -25 °C for 15 minutes before allowing the reaction to

warm to room temperature overnight. The white precipitate was removed by filtration through a medium fritted glass funnel, and the filtrate was concentrated to a yellow foam. Chromatography, with methanol:dichloromethane (gradient, 0:100, 2:98) as the eluent, gave a yellow foam (0.58 g), which was dried overnight to give the title compound.

Henceforth this procedure will be referred to as Coupling Method B.

The intermediate 3-benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydropyridylacetic acid was prepared as follows:

a. 3-Aza-4-phenylpent-3-enal dimethyl acetal. Acetophenone (60.6 g) and aminoacetaldehyde dimethyl acetal (78.9 g) were dissolved in toluene (650 mL) in a 1 L round-bottomed flask. A Dean-Stark trap, fitted with a reflux condenser, was attached to the reaction vessel and the solution was brought to reflux. The trap was drained after 17, 41, and 48 hours (30 mL each time). After 65 hours, the mixture was cooled and volatiles were evaporated to leave a yellow liquid (103.3 g). Fractional distillation gave two major fractions: fraction 1, 10.5 g (60-126 °C, 20-24 Pa); fraction 2, 78.66 g (126-130 °C, 17-20 Pa). Fraction 1 contained a significant amount of acetophenone and amino acetaldehyde dimethyl acetal. Fraction 2 contained less than 5% acetophenone and acetal, and was used directly in the next step. The NMR spectrum was obtained from a clean fraction of imine produced in a different run; 300 MHz NMR: 2.20 (s,3), 3.33 (s,6), 3.54 (d,2), 4.70 (t,1), 7.38-7.43 (m,3), 7.79-7.82 (m,2).

b. Dimethyl 4-aza-6,6-dimethoxy-3-phenylhex-2-enylidine-malonate. A dry, 2 L, 3-necked flask was equipped with a mechanical stirrer, an addition funnel and a Claisen adapter fitted with a thermometer and a nitrogen inlet. To the reaction vessel was added a solution of lithium diisopropylamide (230 mL, 2.0 M in hexane/-tetrahydrofuran) and tetrahydrofuran (700 mL). To the cooled (5 °C) solution was added the crude material from Example 1.a. (78.5 g) in

tetrahydrofuran (150 mL) over 30 minutes. The internal temperature was maintained at 5 °C during the addition and for 45 minutes thereafter. A solution of dimethyl methoxymethylenemalonate (70.5 g) in dry tetrahydrofuran (150 mL) was added dropwise over 30 minutes. The dark amber reaction mixture was allowed to warm to room temperature and was stirred overnight. The mixture was diluted with dichloromethane (2 L) and washed (saturated ammonium chloride). The aqueous washes were back extracted with dichloromethane. The combined dichloromethane layers were washed (brine) and dried ($MgSO_4$). Evaporation gave the crude diene ester (147.6 g) as a red oil. This material was used without further purification. A separate iteration of this procedure provided a clean sample for characterization after chromatography; chromatography solvent: ethyl acetate:chloroform (5:95); TLC: R_f=0.32, ethyl acetate:chloroform:methanol (5:95:1); 300 MHz NMR: 3.33 (s,6), 3.48 (s,3), 3.68 (s,3), 4.63 (broad s,1), 6.17 (d,1), 7.33-7.35 (m,3), 7.52-7.54 (m,3), 7.90 (broad s,1); MS: m/z=350(M+1).

c. 1-(2,2-Dimethoxyethyl)-6-phenylpyrid-2-one-3-carboxylic acid. A 3 L round-bottomed flask was equipped with a stir bar and fitted with a Claisen adapter holding a thermometer and a nitrogen inlet. The flask was charged with a solution of the product from Example 1.b. in methanol (1.5 L). Sodium methoxide (32.4 g) was added in one portion and caused a mild warming. After 3 hours, aqueous sodium hydroxide (750 mL, 10% w/v) was added to the mixture in one portion. The mixture was stirred at room temperature for 2 hours, the methanol was evaporated, and the aqueous residue was acidified with hydrochloric acid and extracted with dichloromethane. The extracts were washed (brine), dried ($MgSO_4$), and evaporated to give a red-brown oil (99.6 g) which partially solidified. This material was used without further purification. A sample of the pyridone, after purification, was characterized; TLC: R_f=0.41, methanol:chloroform:-acetic acid (1.5:98:0.5); 300 MHz NMR: 3.13 (s,6), 4.14 (d,2), 4.63 (t,1), 6.64 (d,1), 7.51-7.58 (m,5), 8.41 (d,1).

d. 3-Benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridylacetaldehyde dimethyl acetal. An oven-dried, 3 L, three-necked flask was equipped with a mechanical stirrer, a thermometer and a reflux condenser capped with a nitrogen inlet. The reaction vessel was charged with a dioxane (1 L) solution of the product from Example 1.c. (99.6 g). Diphenylphosphoryl azide (103.9 g) and triethylamine (39.8 g) were each added to the reaction vessel in one portion and washed down with dioxane (50 mL each). The resulting solution was heated at gentle reflux (100 °C) for 1 hour. Gas evolution was vigorous at first but then subsided. The reaction mixture was cooled to 70 °C, and benzyl alcohol (38.9 g) was added in one portion along with a dioxane wash (100 mL). The reaction was heated at reflux for 18 hours, cooled and evaporated. The residual oil was dissolved in ethyl acetate (1 L) and washed with 1 N hydrochloric acid:brine (1:1), followed by brine. The organic layer was dried ($HgSO_4$) and evaporated to give the crude mixture (249.5 g). This material was purified by chromatography, with ethyl acetate:-dichloromethane (gradient, 0:100, 5:95) as the eluent, to yield the amide (43.1 g); TLC: R_f=0.49, ethyl acetate:chloroform (5:95); 300 MHz NMR: 3.09 (s,6), 4.02 (d,2), 4.54 (t,1), 5.19 (s,2), 6.19 (d,1), 7.34-7.50 (m,5), 7.89 (d,1), 8.54 (s,1).

e. 3-Benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridylacetaldehyde. The product from Example 1.d. (43.1 g) was dissolved in a mixture of tetrahydrofuran (700 mL) and 3N aqueous hydrochloric acid (225 mL). The mixture was held at reflux under nitrogen for 3.5 hours. The mixture was cooled and the tetrahydro-furan was evaporated. The aqueous residue was extracted with dichloromethane, washed (saturated aqueous sodium bicarbonate) and dried ($HgSO_4$). Evaporation gave the crude product as a tan solid. Trituration with ether (300 mL) gave the aldehyde (27.3 g) as a white solid; TLC: R_f=0.32, ethyl acetate:dichloromethane (5:95); 300 MHz NMR: 4.66 (s,2), 5.19 (s,2), 6.28 (d,1), 7.32-7.49 (m,10), 7.94 (d,1), 8.61 (s,1), 9.50 (s,1); MS: m/z=363(M+1).

f. 3-Benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridylacetic acid. A 2 L, three-necked flask was equipped with a mechanical stirrer, an addition funnel and a Claisen adapter holding a thermometer and a reflux condenser capped with a nitrogen inlet. The flask was charged with a tetrahydrofuran (275 mL) solution of the product from Example 1.e. (40.5 g). The addition of tert-butanol (275 mL) caused precipitation of the aldehyde starting material. The reaction mixture was cooled to 15 °C with an ice-water bath, and 2-methyl-2-butene (250 mL) was added in one portion. A solution of sodium chlorite (80%, 88.5 g) and sodium dihydrogen phosphate monohydrate (108.0 g) in water (400 mL) was added dropwise to the reaction mixture over 45 minutes. The internal temperature was maintained at 20 °C during the addition. Stirring at room temperature was continued for 2 hours. The mixture was partially evaporated to leave an aqueous suspension of white solid. The mixture was diluted with brine and extracted with chloroform. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in diethyl ether and evaporated to give an off-white solid, which was triturated with hexane:diethyl ether (9:1) to give the acid as an off-white solid (43.1 g); TLC: R_f=0.20, methanol:dichloromethane (2:98); 300 MHz NMR: 4.44 (s,2), 5.19 (s,2), 5.24 (d,1), 7.33-7.51 (m,10), 7.92 (d,1), 8.59 (s,1), 13.07 (broad s,1); MS: m/z=363(M+1). NMR showed that this material was pure but contained diethyl ether, which was not removed by prolonged drying in a vacuum oven.

The intermediate 2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidin-2-yl)propylammonium trifluoroacetate was prepared using the procedures in Examples 1.g.-1.j. below, which are similar to those described in J. Biol. Chem. (1984), 259, 15106-15114.

g. 2-Isopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolidine. A dry, 5 L, three-necked flask was equipped with a mechanical stirrer, a Claisen adapter holding a low-temperature thermometer and an addition funnel, and a second Claisen adapter holding an addition funnel and a nitrogen inlet. Isopropylmagnesium chloride (1.60 L, 2.0 M in tetrahydrofuran) was transferred via cannula into one addition funnel,

and triethylborate (467.1 g) was placed into the other addition funnel. Tetrahydrofuran (1 L) was placed in the reaction flask and was cooled to -78 °C. The triethylborate and the Grignard reagent were simultaneously added dropwise over a 2 hour period, while maintaining an internal temperature of less than -50 °C. Upon completion of the addition, the mixture was stirred for an additional 2 hours at -78 °C. The reaction was quenched by dropwise addition of concentrated hydrochloric acid (600 mL) over 1 hour. The temperature of the mixture rose from -78 °C to -20 °C, and the dark amber solution became colorless. The mixture was stirred overnight, evaporated, and extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$). Evaporation gave crude (dihydroxy)isopropylborane as a white semi-solid (360.2 g). This material was dissolved in ethyl acetate (1 mL), and the solution was placed in a 3 L, 3-necked flask equipped with a mechanical stirrer and a nitrogen inlet. To the solution was added 2,3-dimethyl-2,3-butanediol (378 g) and anhydrous magnesium sulfate (200 g). The mixture was allowed to stir for 70 hours, the solids were removed by filtration, and the filtrate was evaporated to yield an amber oil. The oil was purified by two fractional distillations at reduced pressure. The fraction (184.9 g) which initially distilled at 60-97 °C (6000 Pa) was redistilled to yield the dioxoborolidine (164.0 g) as a pale yellow oil; bp 74-78 °C (6500 Pa); 300 MHz NMR: 0.87-0.94 (m,7), 1.17 (s,12); MS: m/z=171(M+1).

h. 2-(1-Chloro-2-methylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolidine. A dry, 3 L, three-necked flask was equipped with a mechanical stirrer, a condenser capped with a nitrogen inlet and a Claisen adapter holding a low-temperature thermometer and an addition funnel. Dichloromethane (92.8 g) and tetrahydrofuran (600 mL) were added to the flask and cooled to -78 °C. n-Butyllithium solution (421 mL, 2.5 M in hexanes) was transferred via cannula into the addition funnel. The n-butyllithium was added dropwise over 3 hours while maintaining the internal temperature at -78 °C. The reddish-brown solution was treated with the product from Example 1.g. (128.0 g) by dropwise addition over 10 minutes. The reaction mixture

was stirred for 1 hour while warming slowly to -40 °C. The mixture was cooled to -78 °C and a zinc chloride solution (490 mL, 1.0 M in ether) was added over 15 minutes. The mixture was stirred for 15 minutes at -78 °C and allowed to warm to room temperature overnight. The mixture was evaporated, dissolved in ether, washed (saturated ammonium chloride, water), dried ($MgSO_4$) and evaporated to give a brown oil (149.2 g). Fractional distillation under reduced pressure gave the chloride (123.5 g) as a pale yellow oil; bp 105-122 °C (2700 Pa); NMR: 0.92-0.97 (m,6), 1.15-1.23 (m,12), 1.98 (m,1), 3.32 (d,1); MS: m/z=219(M+1).

i. 2-[1-[N,N-Bis(trimethylsilyl)amino]-2-methylpropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolidine. A 2 L, 3-necked flask was equipped with a mechanical stirrer, an addition funnel and a Claisen adapter holding a low-temperature thermometer and a nitrogen inlet. The flask was charged with a tetrahydrofuran (800 mL) solution of 1,1,1,3,3,3-hexamethyldisilazane (120.8 g), and the addition funnel was charged with n-butyllithium solution (300 mL, 2.5 M in hexane). The n-butyllithium was added dropwise to the cooled reaction vessel over 30 minutes. The internal temperature was maintained in the range -78 to -60 °C during the course of the addition. The reaction mixture was warmed to 0 °C for 30 minutes, was cooled to -78 °C, and the product from Example 1.h. (163.5 g) was added dropwise over 15 minutes. When the addition was complete, the cooling bath was removed and the mixture was allowed to warm to room temperature overnight. The orange suspension was filtered to remove solids and the filtrate was evaporated. The residue was filtered to remove solids and the filter cake was washed with ether. Concentration of the filtrate gave an oil which was fractionally distilled at reduced pressure to give the amine (212.8 g) as a colorless oil; bp 96-106 °C (200 Pa); NMR: 0.11 (s,18), 0.86 (m,7), 1.19 (m,12), 1.75 (m,1); MS: m/z=344(M+1).

j. 2-Methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidin-2-yl)-propylammonium trifluoroacetate. A 2 L, 3-necked flask was equipped with a mechanical stirrer, a condenser capped with a nitrogen inlet and a Claisen adapter holding a thermometer and an addition funnel.

The vessel was charged with a hexane (1 L) solution of the product from Example 1.i., the solution was cooled to 3 °C (ice/water bath), and trifluoroacetic acid (226.5 g) was added over 10 minutes. The temperature of the mixture rose to 25 °C over the course of the addition and a white precipitate formed. The mixture was stirred for 1 hour at 5 °C, filtered, and the white solid was collected, washed with hexane, and dried, to afford the ammonium salt (116.8 g) as a white powder; mp 131-133 °C; 300 MHz NMR: 0.95 (t,6), 1.25 (s,12), 1.92-1.97 (m,1), 2.62 (broad s,1), 7.80 (broad s,2); MS: m/z=200(M+1).

EXAMPLE 2. 2-(3-Benzyloxycarbonylamino-2-oxo-1,2-dihydro-1-pyridyl)-N-[2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidin-2-yl)propyl]-acetamide.

3-Benzyloxycarbonylamino-2-oxo-1,2-dihydro-1-pyridylacetic acid (3.5 g) and 2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidin-2-yl)propylammonium trifluoroacetate (4.35 g) were subjected to the conditions of Coupling Method A to afford a mixture that was purified by chromatography, with methanol:chloroform (1:65) as the eluent, to give the title compound as a white solid; TLC: R_f=0.50, methanol:chloroform (1:40); NMR: 0.87 (d,3), 0.89 (d,3), 1.12 (s,12), 1.73-1.80 (m,1), 2.68 (t,1), 4.70 (s,2), 5.16 (s,2), 6.27 (t,1), 7.29-7.44 (m,6), 7.83 (dd,1), 8.40 (s,1), 8.51 (d,1); MS: m/z=484(M+1). Analysis for $C_{25}H_{34}BN_3O_6$: Calculated: C, 62.12; H, 7.09; N, 8.69; Found: C, 62.07; H, 7.06; N, 8.76.

The intermediate 3-benzyloxycarbonylamino-2-oxo-1,2-dihydro-1-pyridylacetic acid was prepared as follows.

a. Ethyl 3-nitro-2-oxo-1,2-dihydro-1-pyridylacetate. A solution of 3-nitropyrid-2-one (20 g) in dimethylformamide (600 mL) was cooled with an ice-water bath and sodium hydride (97%, 4.1 g) was added. Stirring was continued as the reaction warmed to room temperature over 25 minutes. The brown reaction mixture was cooled with an ice-water bath prior to addition of ethyl iodoacetate (20 mL).

Stirring was continued overnight as the mixture warmed to room temperature. The reaction was quenched by dropwise addition of water (250 mL), diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine and dried. Evaporation and overnight drying under vacuum gave the pyridone (33.40 g) as an oil; TLC: R_f=0.43, methanol:dichloromethane (5:95); 300 MHz NMR: 1.22 (t,3, J=7), 4.17 (q,2, J=7), 4.87 (s,2), 6.52 (dd,1, J=6.6, 7.7), 8.20 (dd,1, J=2, 6.6), 8.49 (dd,1, J=2, 7.7); MS: m/z=227(M+1).

b. Ethyl 3-amino-2-oxo-1,2-dihydro-1-pyridylacetate. A solution of the product from Example 2.a. (32.3 g) in ethanol (600 mL) was added to 10% (w/w) palladium on carbon (3.23 g). The mixture was shaken under a hydrogen atmosphere (3.5 bar) for 4 days. The mixture was filtered through diatomaceous earth and evaporated to afford the amine (27.79 g) as an oil; TLC: R_f=0.47, methanol:chloroform (1:40); MS: m/z=197(M+1).

c. Ethyl 3-benzyloxycarbonylamino-2-oxo-1,2-dihydro-1-pyridyl-acetate. Benzyl chloroformate (28 mL) was added dropwise over 10 minutes to a solution of the product from Example 2.b. (27.79 g) in tetrahydrofuran (580 mL) containing sodium carbonate (34.3 g). The brown-grey suspension was allowed to stir overnight, was diluted with 10% hydrochloric acid and extracted with ethyl acetate. The organic extracts were washed (saturated sodium bicarbonate, brine), dried, and evaporated. Trituration with diethyl ether followed by air drying gave the benzyloxycarbonyl compound (21 g) as an off-white solid; TLC: R_f=0.55, ethyl acetate:dichloromethane (5:95); NMR: 1.20 (t,3), 4.14 (q,2), 4.76 (s,2), 5.17 (s,2), 6.31 (t,1), 7.30-7.45 (m,6), 7.87 (dd, 1), 8.50 (s,1); MS: m/z=331(M+1).

d. 3-Benzyloxycarbonylamino-2-oxo-1,2-dihydro-1-pyridylacetic acid. A water (35 mL) solution of sodium hydroxide (3.09 g) was added to a solution of the product from Example 2.c. (20.8 g) in tetrahydro-furan:ethanol (600 mL, 1:1). After 1 hour, the mixture was evaporated, diluted with water, and brought to pH 2 with 10% hydrochloric acid. The solid was isolated by filtration, washed

(water, followed by ether), and dried overnight in a vacuum oven at 40 °C, to yield the acid (17.11 g) as a white solid; NMR: 4.68 (s,2), 5.17 (s,2), 6.29 (t,1, J=7), 7.30-7.45 (m,6), 7.86 (dd,1, J=1.7, 7), 8.46 (s,1); MS: m/z=303(M+1).

EXAMPLE 3. 2-(3-Amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-[2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidine-2-yl)propyl]-acetamide.

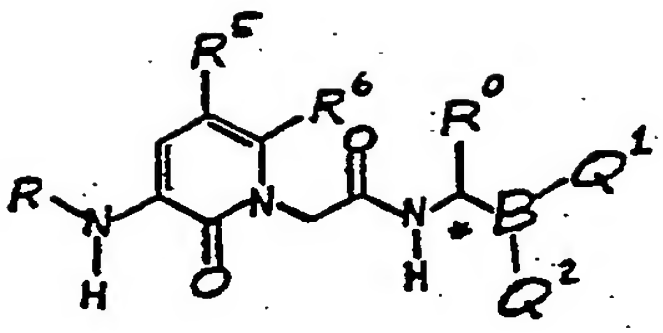
To a solution of 2-(3-benzyloxycarbonylamino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-[2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidin-2-yl)propyl]acetamide (0.28 g) in tetrahydrofuran (5 mL) was added 10% (w/w) palladium on carbon (0.097 g) and the suspension was stirred under hydrogen overnight. The mixture was filtered through diatomaceous earth, evaporated, and purified by chromatography, with methanol:dichloromethane as the eluent (1:50), to give the title compound (0.13 g) as a white solid; TLC: R_f=0.36, methanol:chloroform (1:20); 300 MHz NMR: 0.85 (t,6), 1.15 (s,12), 1.70-1.80 (m,1), 2.51 (broad d,1), 4.38 (q,2), 5.19 (broad s,2), 5.98 (d,1), 6.51 (d,1), 7.39 (s,5), 8.35 (broad s,1); MS: m/z=426(M+1). Analysis for $C_{23}H_{32}BN_3O_4 \cdot 0.25\ H_2O$: Calculated: C, 64.27; H, 7.62; N, 9.78; Found: C, 64.48; H, 8.04; N, 9.64.

Example 4. 2-[3-(4-Acetamidophenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl]-N-[2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidine-2-yl)propyl]acetamide.

To a solution of 2-(3-amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-[2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidine-2-yl)propyl]acetamide (0.5 g) and pyridine (0.46 g) in tetrahydrofuran (10 mL) was added 4-acetamidophenylsulfonyl chloride (0.35 g), and the resulting solution was allowed to stir for 4 hours. The reaction mixture was diluted with ethyl acetate, washed (water, brine), dried ($MgSO_4$) and evaporated. Chromatography, with tetrahydrofuran:dichloromethane (gradient, 5:95 to 15:85) as the eluent, gave the title compound (0.41 g); TLC: R_f=0.6,

tetrahydrofuran:dichloromethane (20:80). Analysis for $C_{31}H_{39}BN_4O_7S \cdot 0.25\ H_2O$: Calculated: C, 59.38; H, 6.35; N, 8.93; Found: C, 59.64; H, 6.65; N, 8.55.

FORMULAE



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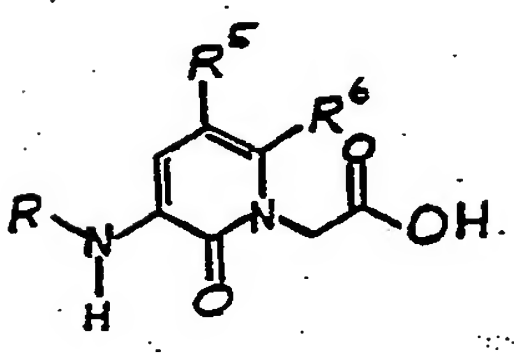

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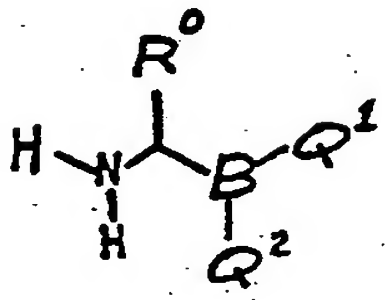

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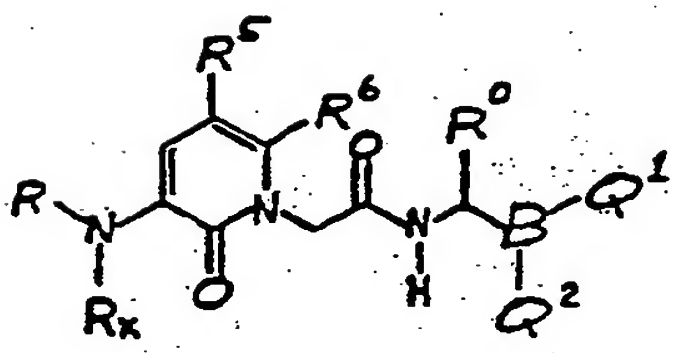
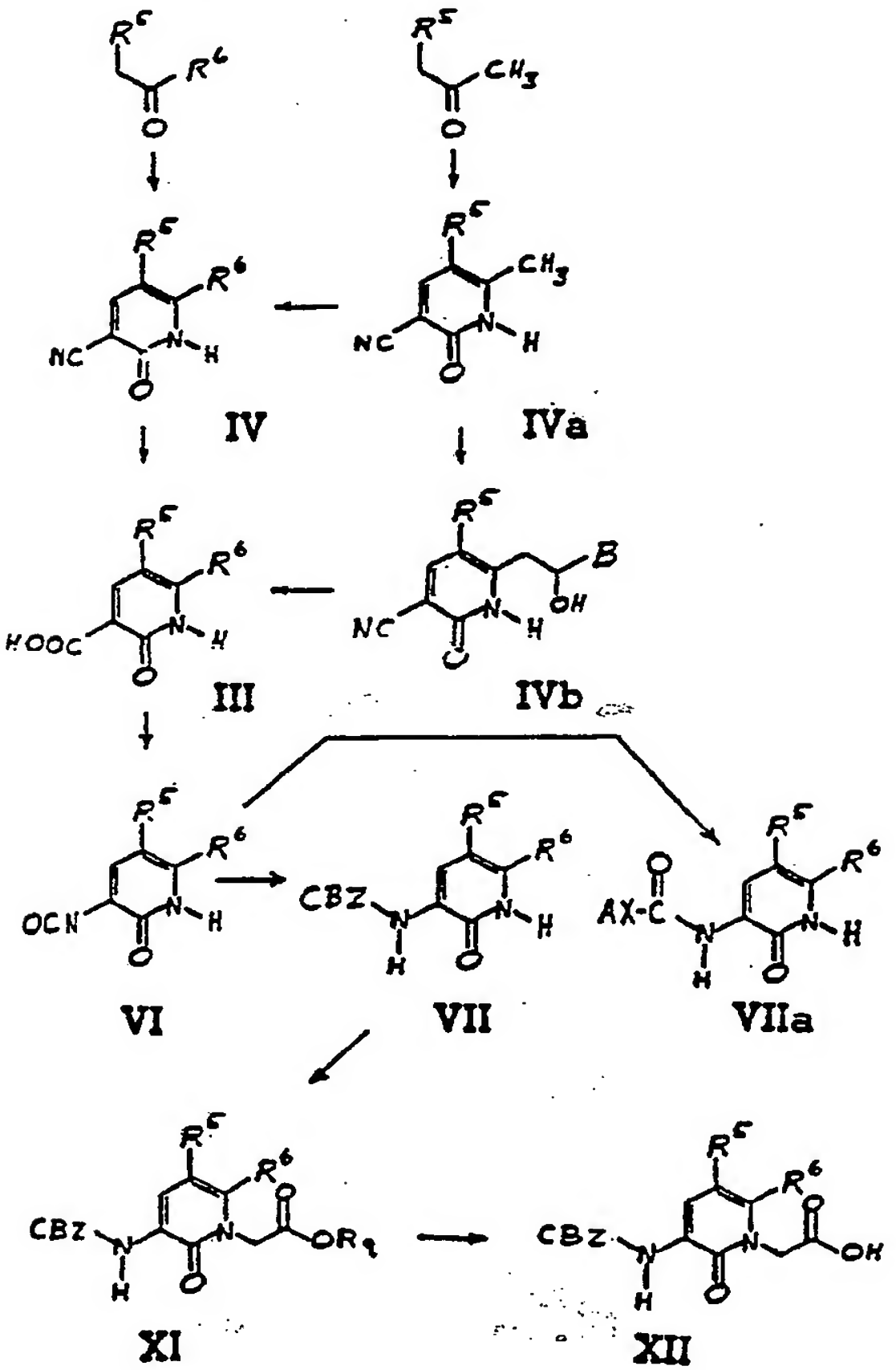


Vb

SCHEME I



SCHEME II

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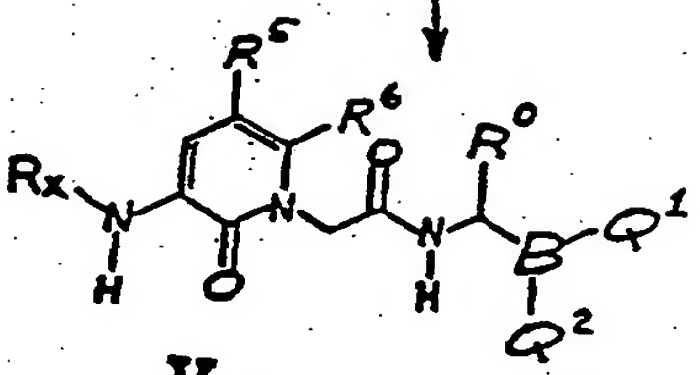
↓

I, R = H

↓



Va

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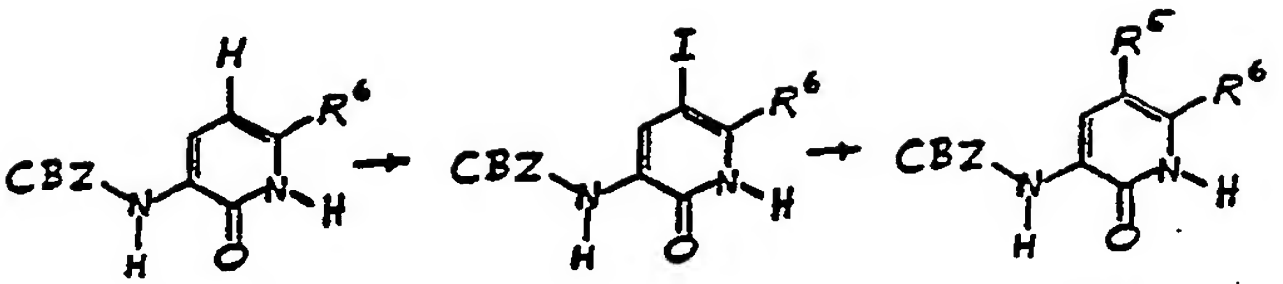
Vb

SCHEME III

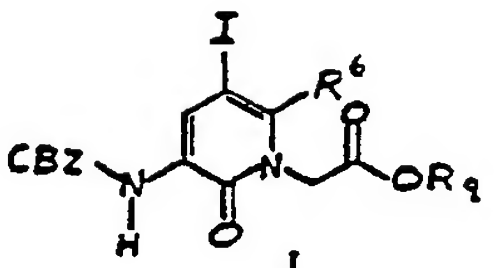


VII

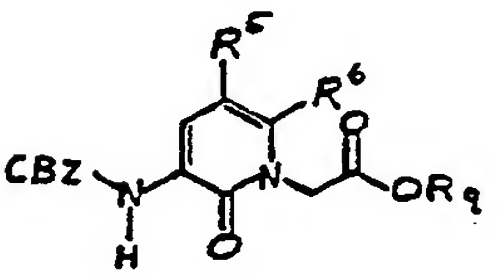
$R^5 = H$

XXI

VII

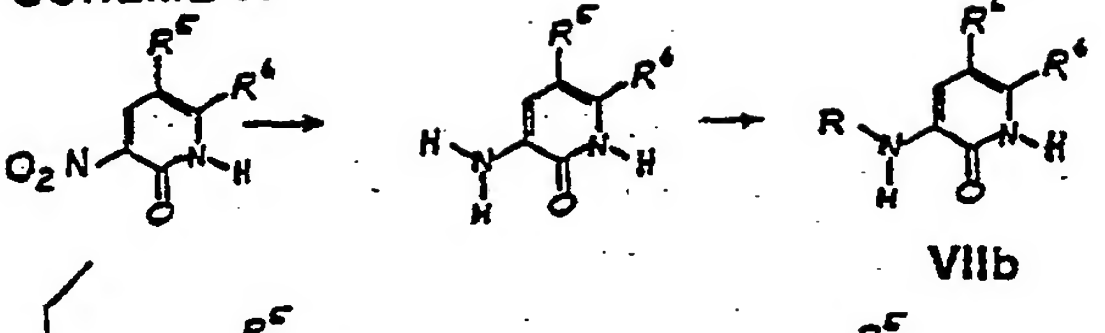


XXIII



XI

SCHEME IV



What is claimed is:

1. A compound of formula I (formula set out hereinbelow) wherein:

R^0 is (1-5C)alkyl;

R is hydrogen; or

R is an acyl group of formula A.X.CO- in which A.X-, taken together, is hydrogen, trifluoromethyl, 2,2,2-trifluoroethoxy, amino, methoxyamino, 2,2,2-trifluoroethylamino, RbRcN.O-, RaOCONH-, R^1SO_2NH-, RaOCO-, RbRcNCO- or RaCO-; or

R is an acyl group of formula A.X.CJ- in which

J is oxygen or sulfur;

X is a direct bond, imino, oxy or thio; and

A is as defined below or

A is tetrahydropyran-4-yl, 1-methylpiperid-4-yl, or 5-methyl-1,3-dioxacyclohex-5-ylmethyl; or

R is a sulfonyl group of formula D.W.SO_2- in which D.W-, taken together, is hydroxy, amino, di(lower alkyl)amino, 2,2,2-trifluoroethylamino, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl or trifluoromethyl; or

W is a direct bond, imino, carbonylimino, oxycarbonylimino or iminocarbonylimino; and

D is as defined below; or

R is a group G as defined below;

The group A, D or G is (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-3C)alkyl, aryl, aryl(1-3C)alkyl, heteroaryl or heteroaryl(1-3C)-alkyl wherein an aryl or heteroaryl moiety may bear one or more halogeno, nitro, methyl or trifluoromethyl groups and further wherein the group A, D or G may bear one or more substituents selected from a group consisting of hydroxy, lower alkoxy, lower acyloxy, COORa, CH_2COORa, CONRbRc, CH_2CONRbRc, $COO(CH_2)_2NReRf$, cyano, SO_2R^1, $CONRdSO_2R^1$, NReRf, NRgCHO, $NRgCOR^2$, $NRgCOOR^2$, NRhCQNRiRj, $NRkSO_2R^3$, SO_2NRlRm, SO_2NRnCOR^4 and P(O)$(ORa)_2$ in which

Q is oxygen or sulfur;

Ra-Rn are independently hydrogen, benzyl or lower alkyl; or, independently, a group NRbRc, NReRf, NRiRj or NRlRm is a cyclic

radical selected from a group consisting of 1-pyrrolidinyl, piperidino, morpholino or 1-piperazinyl which may bear a lower alkyl substituent at the 4-position; or, independently, a group NReRf is a cyclic radical selected from a group consisting of 2-pyrrolidinon-1-yl, succinimido, oxazolidin-2-on-3-yl, 2-benzoxazolinon-3-yl, phthalimido and cis-hexahydrophthalimido; and

R^1-R^4 are independently trifluoromethyl, (1-6C)alkyl, (3-6C)cycloalkyl, aryl or heteroaryl in which the aryl or heteroaryl may bear one or more substituents selected from a group consisting of lower alkyl, hydroxy, lower alkoxy, halogeno or trifluoromethyl;

Each of R^5 and R^6 is, independently, hydrogen or lower alkyl; or

One of R^5 and R^6 is hydrogen or methyl and the other of R^5 and R^6 is a radical of formula E.Y- in which

E is aryl or heteroaryl, which aryl or heteroaryl independently may bear one or more of the substituents defined for A, D or G or an aryl or heteroaryl moiety thereof;

Y is a direct bond, methylene, ethylene or trans-vinylene;

Q^1 and Q^2, which may be the same or different, is each hydroxy or OR^7, or when taken together from a moiety derived from a physiologically acceptable dihydroxy compound having at least two hydroxy groups separated by at least two connecting atoms in a chain or ring, said chain or ring comprising carbon atoms, and optionally, a heteroatom or atoms which can be O, S or N, wherein R^7 is (1-10C)alkyl, (3-10C)cycloalkyl, benzyl or phenyl in which benzyl or phenyl the ring may bear one or more halogeno, lower alkyl or lower alkoxy substituents; and

provided that no aliphatic carbon is bonded to more than one nitrogen or oxygen, except as part of a cyclic ketal or where the nitrogen bears a carbonyl group; or,

for a compound of formula I which is acidic or basic, a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1 wherein R^0 is ethyl or isopropyl; W is a direct bond or imino; G is (1-3C)alkyl, aryl(1-C)alkyl or heteroaryl(1-2C)alkyl which may bear one or more

substituents as defined in Claim 1 for G or a part thereof;

(1-6C)alkyl or (1-10C)alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, 3-methylbutyl, 1-ethylpropyl, hexyl or 4-methylpentyl; (3-6C)cycloalkyl or (3-10C)cycloalkyl is cyclopropyl, cyclopentyl or cyclohexyl; the (1-3C)alkyl portion of (3-6C)cycloalkyl-(1-3C)alkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl is methylene, ethylene or trimethylene; aryl is phenyl, indenyl, indanyl or naphthyl; heteroaryl is furyl, imidazolyl, tetrazolyl, pyridyl (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl or quinolinyl (or its N-oxide); lower alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; lower acyloxy is acetoxy; lower alkoxy is methoxy, ethoxy, propoxy, isoproxy or t-butoxy; halogeno is bromo, chloro or fluoro;

COORa is carboxy or methoxycarbonyl; $NRgCOR^2$ is trifluoroacetylamino; $CONRdSO_2R^1$ is N-phenylsulfonylcarbamoyl or N-(4-chlorophenylsulfonyl)carbamoyl; A.X-, taken together, is tris(hydroxymethyl)methylamino, tris(acetoxymethyl)methylamino or 2,2-bis(hydroxymethyl)propoxy;

Q^1 and Q^2 are each hydroxy, methoxy, ethoxy or isopropoxy; or Q^1 and Q^2, taken together, are the residue derived from 2,3-butanediol, 2,3-dimethyl-2,3-butanediol, 1,3-propanediol, diethanolamine, catechol, (1R,2R,3S,5R)-(-)- or (1S,2S,3R,5S)-(+)-pinanediol, or 2,5-dimethylhexan-3,4-diol.

3. A compound as claimed in Claim 1 or 2 wherein R^0 is isopropyl; J is oxygen; X is a direct bond, imino or oxy; A is methyl, ethyl, phenyl, benzyl, phenethyl, pyridyl, thienyl, 5-tetrazolyl, thiazolyl, pyridylmethyl, thenyl, 5-tetrazolylmethyl, 2-(pyridyl)ethyl, 2-(thienyl)ethyl or 2-(thiazolyl)ethyl wherein the phenyl or heteroaryl group may bear one or two halogeno or methyl groups and further wherein the group A may bear a substituent selected from hydroxy, methoxy, t-butoxy, acetoxy, pivaloyloxy, carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, dimethylcarbamoyl, 2-(dimethylamino)ethoxycarbonyl, cyano, methylsulfonyl, phenylsulfonyl, N-methylsulfonylcarbamoyl, N-phenylsulfonylcarbamoyl, amino, dimethylamino, oxazolidin-2-on-3-yl, acetylamino,

trifluoroacetylamino, ureido, methylsulfonyl, sulfamoyl, dimethylphosphoryl or diethylphosphoryl; D is methyl, ethyl, isopropyl, tert-butyl, cyclohexyl, phenyl, benzyl, phenethyl, pyridyl, thienyl, 5-tetrazolyl, thiazolyl, quinolinyl, pyridylmethyl, thenyl, 5-tetrazolylmethyl, 2-(pyridyl)ethyl, 2-(thienyl)ethyl or 2-(thiazolyl)ethyl wherein the phenyl or heteroaryl group may bear one or two halogeno or methyl groups and further wherein the group D may bear a substituent selected from hydroxy, methoxy, t-butoxy, acetoxy, pivaloyloxy, carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, dimethylcarbamoyl, 2-(dimethylamino)ethoxycarbonyl, cyano, methylsulfonyl, phenylsulfonyl, N-methylsulfonylcarbamoyl, N-phenylsulfonylcarbamoyl, N-(4-chlorophenylsulfonyl)carbamoyl, methylsulfonylamino, amino, dimethylamino, oxazolidin-2-on-3-yl, acetylamino, trifluoroacetylamino, ureido, methylsulfonyl, sulfamoyl, dimethylphosphoryl or diethylphosphoryl; G is methyl, ethyl, benzyl, phenethyl, pyridyl, pyridylmethyl, thenyl, 5-tetrazolylmethyl, or 2-(pyridyl)ethyl, wherein an alkyl carbon may bear an oxo group and wherein the phenyl or heteroaryl group may bear one or two halogeno or methyl groups and further wherein the group G may bear a substituent selected from hydroxy, methoxy, acetoxy, carboxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl, dimethylcarbamoyl, phenylcarbamoyl, pyridylcarbamoyl, methylsulfonylamino, amino, dimethylamino, acetylamino, nicotinoylamino, or trifluoroacetylamino; and

Q^1 or Q^2 is each methoxy or ethoxy; or Q^1 and Q^2, taken together, are the residue derived from 2,3-dimethylbutane-2,3-diol or 1,3-propanediol.

4. A compound as claimed in Claim 1, 2 or 3 wherein R is hydrogen, trifluoroacetyl, hydroxyoxalyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, 4-fluorophenoxycarbonyl, 4-bromophenoxycarbonyl, 4-methoxyphenoxycarbonyl, benzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-pyridylmethoxycarbonyl, 3-methylpyrid-4-ylmethoxycarbonyl, 2,6-dimethylpyrid-4-ylmethoxy-carbonyl, 2-pyridylmethoxycarbonyl, 6-methylpyrid-2-ylmethoxycarbonyl, 2-dimethylaminoethoxycarbonyl, acetyl, carbamoylmethylaminocarbonyl, 4-(N-phenylsulfonylcarbamoyl)phenylacetyl, sulfo, aminosulfonyl,

dimethylaminosulfonyl, trifluoromethylsulfonyl, methylsulfonyl (which may bear a methoxycarbonyl, carboxy or ethylsulfonyl substituent), methylaminosulfonyl, isopropylaminosulfonyl, butylsulfonyl, butylaminosulfonyl, tert-butylaminosulfonyl, cyclohexylaminosulfonyl, phenylsulfonyl (in which the phenyl may bear a chloro, nitro, amino, acetylamino, trifluoroacetylamino, methoxy, carboxy, N-(4-chlorophenylsulfonyl)carbamoyl, or methylsulfonylamino substituent at the 3- or 4-position), anilino, pyridylsulfonyl, quinolinylsulfonyl, benzylsulfonyl (in which the phenyl ring may bear a nitro or amino substituent at the 3- or 4-position), pyridylmethylsulfonyl, 2-(pyridyl)ethylsulfonyl, benzylaminosulfonyl, methyl, ethyl, benzyl, phenethyl or pyridylmethyl.

5. A compound as claimed in any one of Claims 1-4 in which R^5 is hydrogen and R^6 is hydrogen.

6. A compound as claimed in any one of Claims 1-4 in which R^5 is benzyl, the phenyl ring of which may bear a 3-fluoro, 4-fluoro, 4-trifluoromethyl, 4-methoxycarbonyl, 3-acetoxy, 3-hydroxy, 3-pivaloyloxy, 4-hydroxy, 4-pivaloyloxy, 3-trifluoroacetylamino or 3-amino substituent, and R^6 is hydrogen.

7. A compound as claimed in any one of Claims 1-4 in which R^5 is hydrogen, and R^6 is 2-furyl, 2-thienyl, 3-pyridyl or phenyl in which the phenyl may bear one or two halogeno, trifluoromethyl, methyl, hydroxy, methoxy, tert-butoxy, methoxycarbonyl or carboxy substituents.

8. A compound as claimed in Claim 7 wherein R^6 is phenyl, 4-fluorophenyl or 2-thienyl.

9. A compound as claimed in Claim 1 selected from 2-(3-amino-2-oxo-6-phenyl-1,2-dihydro-1-pyridyl)-N-[2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidine-2-yl)propyl]acetamide and 2-[3-(4-acetamidophenylsulfonylamino)-2-oxo-6-phenyl-1,2-dihydro-

1-pyridyl]-N-[2-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolidine-2-yl)propyl]acetamide, or a pharmaceutically acceptable salt thereof.

10. A salt as claimed in Claim 1 selected from

(a) for an acidic compound of formula I, an alkalai metal salt, an alkaline earth metal salt, an aluminum salt, an ammonium salt, or a salt made from an organic base which affords a pharmaceutically acceptable cation; and

(b) for a basic compound of formula I, an acid-addition salt made with an acid which provides a pharmaceutically acceptable anion.

11. A method of making a compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1-10 which is characterized by:

(A) Coupling a corresponding acid of formula IIa, or an activated derivative thereof, with a corresponding amine of formula IIb, using a conventional coupling method;

(B) For a compound of formula I which contains an N-H residue, removal by using a conventional method of the nitrogen protecting group of a corresponding compound bearing a conventional nitrogen protecting group to afford the compound of formula I which contains an amino N-H residue, including for a compound of formula I in which R is hydrogen, removal of a group from a corresponding compound of formula I, or for a compound of formula I in which R has a value of G, the removal of an activating/protecting group Rx from a corresponding compound of formula Vb;

(C) For a compound of formula I wherein R is an acyl group, acylation of a corresponding amine of formula I wherein R is hydrogen;

(D) For a compound of formula I wherein R is a sulfonyl group, sulfonylation of a corresponding amine of formula I wherein R is hydrogen with a corresponding sulfonic acid of formula D.W.SO_2.OH, or an activated derivative thereof;

(E) For a compound of formula I in which R is a group G, substitution of the group L of a corresponding compound of formula G-L, wherein L is a conventional leaving group, with a corresponding

amine of formula I wherein R is hydrogen, optionally using a conventional catalyst;

(F) For a compound of formula I which bears a hydroxy substituent on an aryl or heteroaryl group, cleaving the alkyl ether or acyloxy ester of a corresponding compound of formula I which bears a lower alkoxy or lower acyloxy substituent on an aryl or heteroaryl group;

(G) For a compound of formula I which bears a group of formula COORa in which Ra is hydrogen (a carboxy group), decomposing the ester group of a corresponding ester made with a conveniently removed acid protecting group, including a corresponding compound of formula I in which Ra is not hydrogen;

(H) For a compound of formula I bearing a moiety of formula COORa, CH_2COORa, CONRbRc, $CH_2CONRbRc$, $COO(CH_2)_2NReRf$ or $CONRdSO_2R^1$, acylation of a corresponding compound of formula HORa, HNRbRc, $HO(CH2)_2NReRf$ or $HNRdSO_2R^1$ with a corresponding acid of formula I bearing a moiety of formula COORa in which Ra is hydrogen, or an activated derivative thereof;

(I) For a compound of formula I bearing a lower acyloxy group or a group of formula NRgCHO, $NRgCOR^2$, $NRgCOOR^2$, NRhCQNRiRj or $NRkSO_2R^3$, acylation or sulfonylation of a corresponding compound of formula I bearing a hydroxy group or an amino group of formula NHRg, NHRh or NHRk (i.e. an amino group of formula NReRf is which Re is hydrogen and Rf is Rg, Rh or Rk) with an activated derivative of a corresponding acid of formula HOCHO, $HOCOR^2$, $HOCOOR^2$, HOCQNRiRj (including an isocyanate or isothiocyanate) or $HOSO_2R^3$, respectively, using a conventional method;

(J) For a compound of formula I which bears a heteroaryl N-oxide group, oxidation of a corresponding compound of formula I which bears a heteroaryl group using a conventional oxidant;

(K) For a compound of formula I which bears a primary amino group, reduction of a corresponding compound bearing a nitro group using a conventional reducing method;

(L) For a compound of formula I in which Q^1 and/or Q^2 is hydroxy, conversion of the corresponding group Q^1 and/or Q^2 of a

compound of formula I in which Q^1 and/or Q^2 is not hydroxy into a hydroxy group by a conventinal method; and

whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of an acidic or basic compound of formula I is required, by reacting the acidic or basic form of such a compound of formula I with a base or acid affording a physiologically acceptable counterion or by any other conventional procedure; and

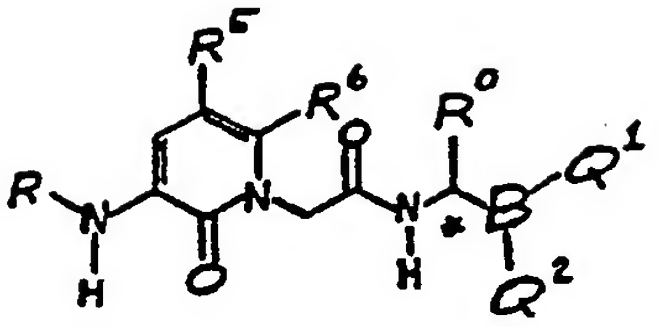
wherein the chemical formulae I, IIa, IIb and Vb are set out hereinbelow; and

wherein each of Q^1, Q^2, R, R^0, R^5, R^6, D, W, G, Ra-Rn, R^1-R^3 and Q, except where more particularly described, has the meaning defined in any one of Claims 1-10.

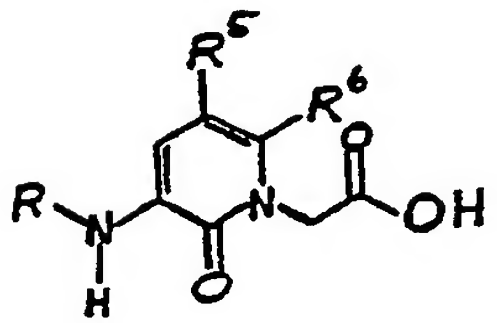
12. A compound of formula Vb, set out hereinbelow, wherein R has a value defined for G in Claim 1; Q^1, Q^2, R^0, R^5 and R^6 are defined as in Claim 1; and Rx is a group which protects and activates a primary amino group for substitution, or a salt thereof.

13. A pharmaceutical composition comprising a compound as defined in Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

FORMULAE



I



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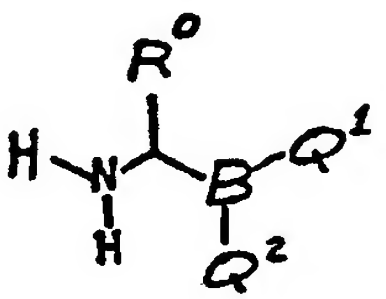
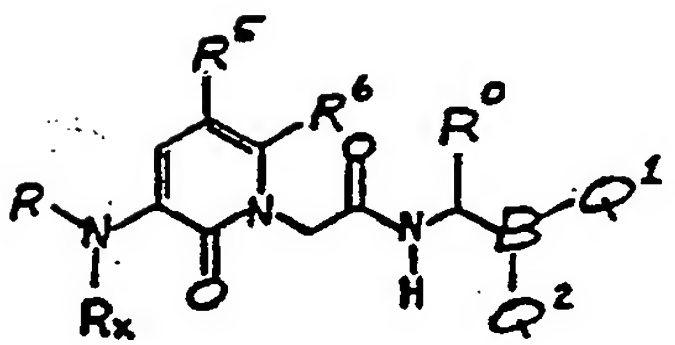


IIb



Vb

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00796

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07K5/06; A61K37/64

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
P,X	EP,A,0 509 769 (ICI AMERICAS INC.) 21 October 1992 see claims; examples	1-13
A	US,A,4 963 655 (D.H. KINDER AND M.M. AMES) 16 October 1990 see column 4, line 60 - column 5, line 14; claims	1,13
A	EP,A,0 315 574 (HOECHST AKTIENGESELLSCHAFT) 10 May 1989 see page 2, paragraph 1 -paragraph 3; claims; examples	1,13

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06 JULY 1993	03. 08. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FUHR C.K.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300796
SA 73124

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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